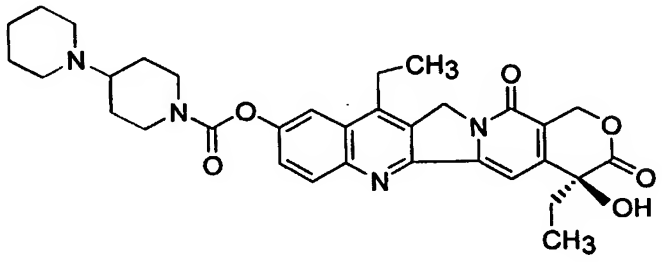
Method of Manufacturing of 7-Ethyl-10-[4-(1-piperidino)-1-piperidino]--carbonyloxycamptothecin

Field of the Invention

This invention relates to a method of manufacturing of 7-ethyl-10-[4-(1-piperidino)--1-piperidino]-carbonyloxycamptothecin of formula I

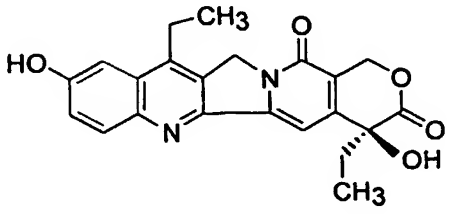


(I)

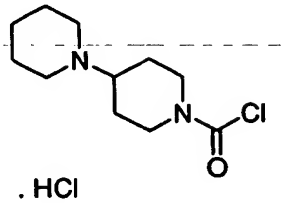
7-Ethyl-10-[4-(1-piperidino)-1-piperidino]-carbonyloxycamptothecin, which is also known as irinotecan base, is used for manufacturing of the cytostatically active irinotecan hydrochloride trihydrate, a topoisomerase inhibitor which is used in treatment of lung and rectum cancer.

Background of the Invention

7-Ethyl-10-[4-(1-piperidino)-1-piperidino]-carbonyloxycamptothecin has been hitherto prepared by condensation of 7-ethyl-10-hydroxycamptothecin of formula



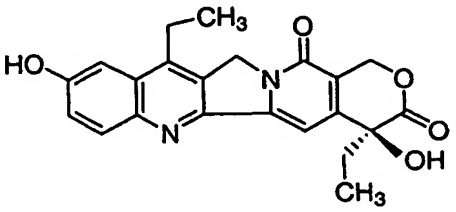
with 1-chlorocarbonyl-4-piperidinopiperidine hydrochloride of formula



in pyridine at room temperature. This method of preparation has been described in US 4 604 463. However, this method of preparation of irinotecan base suffers from the fact that in the condensation coloured impurities are formed which have to be removed by adsorption on a silica gel column and subsequent recrystallization from ethanol. These purification steps are accompanied by substantial losses of the final product and its yields are only about 64 %. Moreover, the method requires distillation of pyridine, extraction of a chloroform layer with sodium carbonate and sodium chloride solutions, and drying of the chloroform layer over magnesium sulfate. Therefore, a better method of preparation of irinotecan base was needed. Such a goal has been achieved by the method according to the present invention.

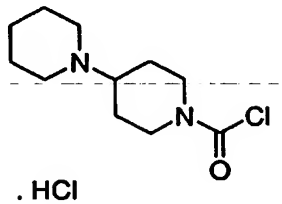
Summary of the Invention

The present invention relates to a method of manufacturing of 7-ethyl-10-[4-(1-piperidino)--1-piperidino]-carbonyloxycamptothecin of formula I, characterized in that 7-ethyl--10-hydroxycamptothecin of formula II



(II)

is condensed with 1-chlorocarbonyl-4-piperidinopiperidine hydrochloride of formula III



(III)

. HCl

in a polar aprotic solvent such as acetonitrile and in the presence of 4-dimethylaminopyridine. The condensation proceeds in suspension, where the polar aprotic solvent dissolves only 4-dimethylaminopyridine whereas 7-ethyl-10-hydroxycamptothecin and 1-chlorocarbonyl-4-piperidinopiperidine hydrochloride in this polar aprotic solvent remain undissolved. The amount of 1-chlorocarbonyl-4-piperidinopiperidine hydrochloride employed in the condensation reaction is preferably 1.3 to 3 mol, more preferably 1.6 to 1.9 mol, per 1 mol of 7-ethyl-10-hydroxycamptothecin. The amount of 4-dimethylaminopyridine used in the condensation ranges preferably between 1.5 and 4 mol, more preferably between 1.8 and 2.2 mol, per 1 mol of 7-ethyl-10-hydroxycamptothecin. The amount of the polar aprotic solvent used in the condensation is preferably 400 to 600 mol, more preferably 430 to 460 mol, per mol of 7-ethyl-10-hydroxycamptothecin. The condensation is performed preferably at a temperature from 70 to 80 °C, more preferably at 73 to 77 °C.

After end of the condensation, the present ballast compounds, consisting of e.g. 4-dimethylaminopyridine, 4-piperidinopiperidine and urea, are removed by washing of the obtained irinotecan base by a polar aprotic solvent, preferably acetonitrile. The yield of the condensation is at least 94 % and the obtained product contains at least 98 % of the desired irinotecan base, as determined by high-performance liquid chromatography.

The main advantage of the method according to this invention consists in that the work-up of the reaction mixture after condensation proceeds only with negligible losses of the final product and that the condensation is not accompanied with coloured impurities.

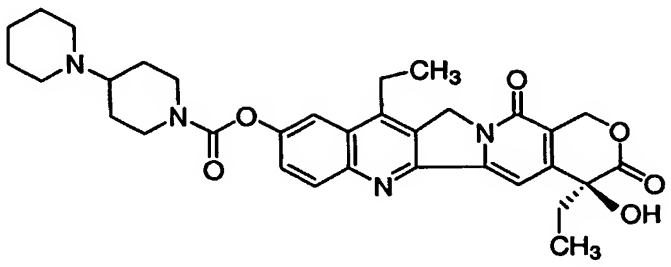
Examples

Example 1

Into a beaker in a sonication bath are placed 10 g (0.0247 mol) of 7-ethyl-10-hydroxy-camptothecin and 99 ml of acetonitrile. The obtained suspension is stirred in the sonication bath to homogeneity. Then the suspension is transferred quantitatively into a three-necked Keller flask equipped with a mechanical stirrer, thermometer and reflux condenser. Into the now empty beaker are now placed 6.2 g (0.0502 mol) of crystalline 4-dimethylaminopyridine and 40 ml of acetonitrile. The mixture is stirred until the crystalline portion dissolves. The obtained solution is then added quantitatively to the suspension of 7-ethyl-10-hydroxy-camptothecin. Into the empty beaker are then added 13.6 g (0.0434 mol) of 1-chlorocarbonyl--4-piperidinopiperidine hydrochloride and 79 ml of acetonitrile and the suspension is stirred in the sonication bath until homogeneous. The obtained suspension is transferred quantitatively into the three-necked Keller flask already containing 7-ethyl-10-hydroxycamptothecin and 4-dimethylaminopyridine in acetonitrile, and 382 ml of acetonitrile is added to the mixture. The obtained reaction suspension in the Keller flask is stirred at 75 °C for 5 h. After 2 h the lightly yellow suspension becomes thicker and its colour turns into a coffee-white one, indicating thus correct course of the reaction. After 5 h, the suspension is cooled to 18 to 20 °C, filtered and the filtration cake is washed with 300 ml of acetonitrile. After removing the acetonitrile by suction filtration, the obtained 7-ethyl--10-[4-(1-piperidino)-1-piperidino]-carbonyloxycamptothecin is dried at 60 to 65 °C to constant weight in a drier. This affords 14.1 g (yield 94.3 %) of product which, according to high-performance liquid chromatography, contains 98.9 % of 7-ethyl-10-[4-(1-piperidino)--1-piperidino]-carbonyloxycamptothecin.

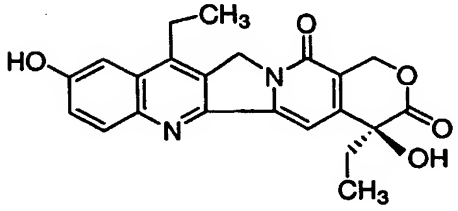
PATENT CLAIMS

1. A method of manufacturing of 7-ethyl-10-[4-(1-piperidino)-1-piperidino]-carbonyloxy-camptothecin of formula I



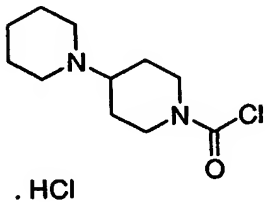
(I)

characterized in that 7-ethyl-10-hydroxycamptothecin of formula II



(II)

is subjected to a condensation reaction with 1-chlorocarbonyl-4-piperidinopiperidine hydrochloride of formula III



. HCl

(III)

in a polar aprotic solvent, e.g. in acetonitrile, in the presence of 4-dimethylaminopyridine.

2. The method according to claim 1, characterized in that 1-chlorocarbonyl--4-piperidinopiperidine hydrochloride is employed in an amount of 1.3 to 3 mol, preferably in an amount of 1.6 to 1.9 mol, per 1 mol of 7-ethyl-10-hydroxycamptothecin.

3. The method according to any of the preceding claims, characterized in that 4-dimethylaminopyridine is employed in an amount of 1.5 to 4 mol, preferably in an amount of 1.8 to 2.2 mol, per 1 mol of 7-ethyl-10-hydroxycamptothecin.

4. The method according to any of the preceding claims, characterized in that the polar aprotic solvent is employed in an amount of 400 to 600 mol, preferably in an amount of 430 to 460 mol, per 1 mol of 7-ethyl-10-hydroxycamptothecin.

5. The method according to any of the preceding claims, characterized in that the condensation reaction is carried out at a temperature of 70 to 80 °C, preferably at a temperature of 73 to 77 °C.